

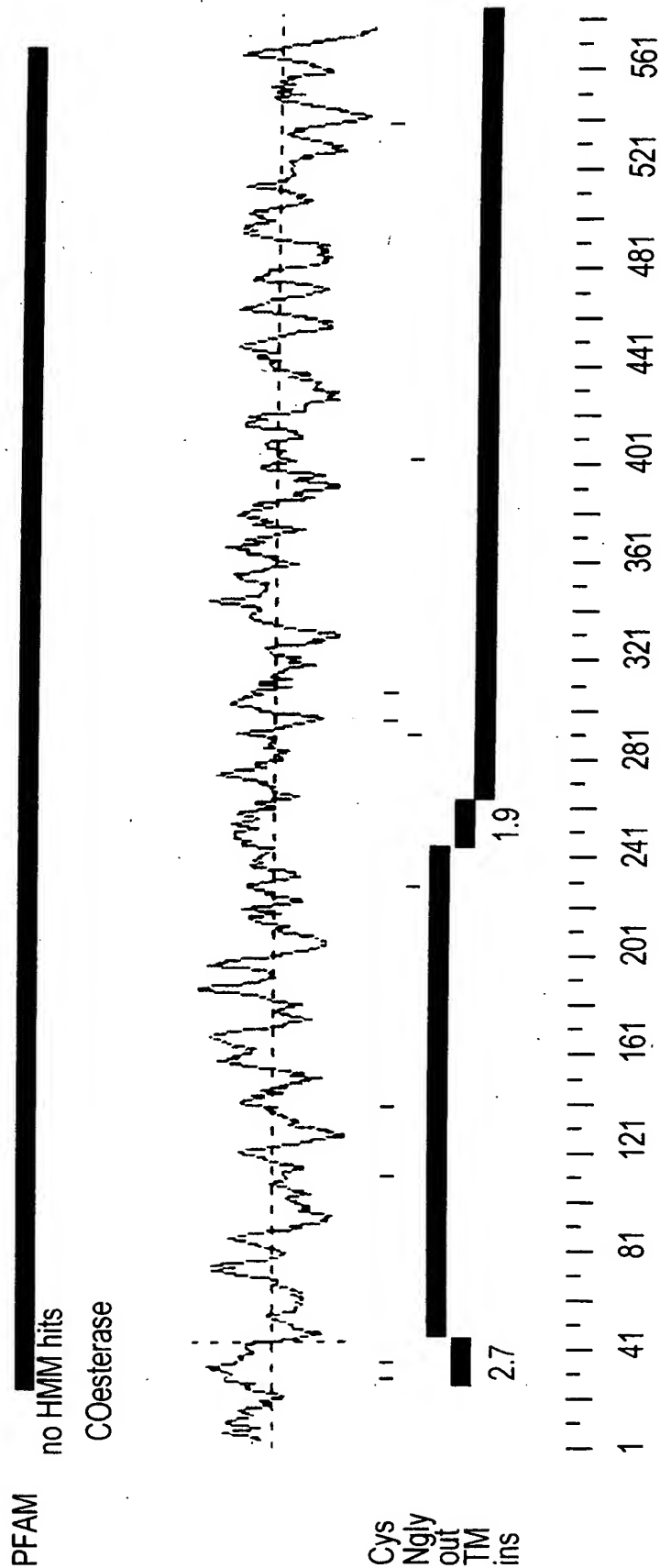


REPLACEMENT SHEET

Applicant: Rosana Kapeller-Libermann, et al.
Title: METHODS OF USING 18903 TO TREAT PAIN AND PAIN-RELATED DISORDERS
Application No.: 10/001,227
Attorney/Agent: Mario Cloutier
Docket No.: MPI00-408PIRM

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FIG. 1





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FIG. 2A

Protein Family / Domain Matches, HMMer version 2

Searching for complete domains in PFAM

hmmpfam - search a single seq against HMM database

HMMER 2.1.1 (Dec 1998)

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HMMER is freely distributed under the GNU General Public License (GPL).

HMM file:

/prod/ddm/seqanal/pfam/pfam6.4/pfam

Sequence file:

/prod/ddm/wspace/orfanal/oa-script.6214.seq

Query: Fbh18903FL

Scores for sequence family classification (score includes all domains):

Model	Description	Score	E-value	N
COesterase	Carboxylesterase	558.6	4.1e-164	1

Parsed for domains:

Model	Domain	seq-f	seq-t	hmm-f	hmm-t	score	E-value
COesterase	1/1	25	569	1	612	558.6	4.1e-164

Alignments of top-scoring domains:

COesterase: domain 1 of 1, from 25 to 569: score 558.6, E = 4.1e-164

*->mvl1lllfl1llllliavlaaakaspdl1VatnnVlcGkvrGvnek

+1+ +L 1 1 ++ +l+a+++ ++ V t++ G++ G++

18903 25 RWILCWSLTLC1MAQTALGALHT---KRPQVVTKY---GTLQCKQMH 65

tdngeqsvysFlGIPYAepFVGnLRFkaPqPykepWsdvldAtkyppsCl

+ ++ +FlG+P+ PP+G LRF +P+P +epW++++dAt+ypp Cl

18903 66 VGKT--PIQVFLGVFSPPLGILRFAPPEP-PEPWKGIRDATTYPGCL 112



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FIG. 2B

18903 113 QdddfgfsldLKvalkmlslgwnklvg...lklSEDCLYLNvytpknt
Q + +g+ 1+++ ++ + + 1 +SEDCLYLNvy P+ +
Q-ESWQ-----LASMYSTREYkWLRFSEDCLYLNvyAPARA 150

18903 151 kpnsklPvMvWihGGGfmgshslplsyldgeslaregnVivVsiNYRL
+ + +lPvMvW +GG+F +G++ s+Y g+ la++++V++V ++ RL
PGDPQLPVMVWFFPGGAFIVGAA-----SSYEGSDLAAREKVVLVFLQHRL 195

18903 196 GplGLstgddklpgsGNyGLlDQrlAlkVWqdnIaaFGGDPnsVTifGe
G++GFLst+d+++ GN+GLlDQ +Al+WVq+NiaaFGGDP++VT+fg+
GIFGFLSTDDSHAR--GNWGLlDQMAALRWVQENIAAFGGDPGNVTLFGQ 243

18903 244 SAGaaSVsl1111sngGDNppsskgLFhRAIsqSGsalspwaigsesnarg
SAGa+S+s l++s p++ gLFhRAIsqSG+al +i+s+ +
SAGAMSISGLIMS-----PLA-SGLFhRAIsqSGTALFRlFITSNP--LK 285

18903 286 rakelarllGCnetsssellldCLRsksaeeLleatrsfllfeyvpflplf
ak++a l+GCn++s l+ CLR s + + + + + f + +f +
VAKKVAHLACNHNSTQILVNCRLALSGTKVMRVS NK-MRFLQlNFQRDP 334

18903 335 l....aFgPvVDGdDapeafipedPeelikeGkfadvPyliGvtdEGgy
++ + +PvVDG+ +ip+dP+ l+ +Gk + vPyl Gv++ E+ +
EeiwSMSPVVDGV-----VIPDDPLVLLTQGVSSVPYLLGVNNLEFNW 379

18903 380 faaml1nasskgedelkketnpdvwllellkyllyfyasealnikmdmddlad
+++++++ + + ket++ l+ 1l+ + +
LLPYIMKFFPLNR-QAMRKETITK-MLWSTRTLLN-ITKEQ-----VP 418

18903 419 kvlekYpgdvddfsvesrkpnlgdmltd1lFkcptrvaadlhakhggsPv
v e+Y++ v + + ++ + d++ D +F+++ + ++ ++++g Pv
LVVEEYLDNVNEHDWKMLRNRMDIVQDATFYA-TLQTAHYHRDAGLPV 467



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FIG. 2C

```
18903 468 YaYvfdhpdgigQflakrvdpefggavHgdEiffvFgnpllleqlyka
      + Y+Y+f h+a+ + v+p+++ga+HgdE++f+Fg p+ ++ 1
      YLYEFEHHAR-----GIIVKPRTDGADHGDEMYFLFGGPFATG-LS-- 507

      teeeeksssktmmywanFAktGnPnngtsnglvWpkytseeqkyslli
      e++ts +mm+ywanFA+tGnP n++ +l+ Wp y+++e +l+
18903 508 MGKEKALS-LQMMKYWANFARTGNP-NDG--NLPCWPRYNKDEK--YLQL 551

      llttitagklkardprkvlcnfw<-*
      +tt +klk+++ ++fw
18903 552 DFTTRVGMKLKEKK-----MAFW 569
```

//

Searching for complete domains in SMART



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FIG. 3A

GAP of: FrGcgManager_76_IOA81nWg_ check: 5132 from: 1 to: 1983

Fbh18903FL - Import - vector trimmed

to: FrGcgManager_76_JOA3WXZ1_ check: 1319 from: 1 to: 2456

z34105 in Patent Nucleotide

Symbol comparison table: /ddm_local/gcg/gcg_9.1/
1/gcgcore/data/rundata/nwsgapdna.cmp
CompCheck: 8760

Gap Weight:	12	Average Match:	10.000
Length Weight:	4	Average Mismatch:	0.000
Quality:	13796	Length:	2746
Ratio:	6.957	Gaps:	14
Percent Similarity:	92.617	Percent Identity:	92.617

Match display thresholds for the alignment(s):

| = IDENTITY
: = 5
. = 1

FrGcgManager_76_IOA81nWg_ x FrGcgManager_76_JOA3WXZ1

..

```
COE-2      1 .....CCT      3
Z34105 101 CATTTCGCCTTGCTGACGGCGTCGAGCCCTGGCCAGACATGTCCACAGGG 150
          4 TTAGCCAATTCGGCCGAGGCCTCCCGCCCCAGTA.CTTGCTGGCAGGGAT 52
          || || | ||| | ||| ||| ||| ||| ||| ||| ||| |||
151 TTCTCCTTCGGGTCCGGGACTCTGGGCTCCACCACCGTGGCCGCCGCGCG 200
          53 TAAGAGCAGA.TAAAAGTGTGCTCACACACTGTAGACACGGCTACCATGC 101
          | |||| | ||| ||| | ||| ||| ||| ||| ||| |||
201 GACCAGCACAGGCGGCGTTTTCTCCTTCGGAACGGGAACGTCTAGCAACC 250
102 CATC.....CACAGTGTGCCATCCACAGTGTGCCATCACTCCTGC. 143
          ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
251 CTTCTGTGGGGCTCAATTTTGGAATCTTGGAAGTACTTCAACTCCAGCA 300
144 .CCACAGCAGGAGCT..GGCTGGAGCATGAGGTGGATTCTGTG..CTGGA 188
          ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
301 ACTACATCTGCTCCTTCAAGTGTTTGGAAACGGGCTCTTTGGATCTAA 350
```




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FIG. 3C

```

766 GGTGCAGGAGAACATCGCAGCCTTCGGGGGAGACCCAGGAAATGTGACCC 815
    ||||||||||||||||||||||||||||||||||||||||||||||||
1050 GGTGCAGGAGAACATCGCAGCCTTCGGGGGAGACCCAGGAAATGTGACCC 1099

816 TGTTTCGGCCAGTCGGCGGGGGGCCATGAGCATCTCAGGACTGATGATGTCA 865
    ||||||||||||||||||||||||||||||||||||||||||||||||
1100 TGTTTCGGCCAGTCGGCGGGGGGCCATGAGCATCTCAGGACTGATGATGTCA 1149

866 CCCCTAGCCTCGGGTCTCTTCCATCGGGCCATTTCCCAGAGTGGCACCGC 915
    ||||||||||||||||||||||||||||||||||||||||||||||||
1150 CCCCTAGCCTCGGGTCTCTTCCATCGGGCCATTTCCCAGAGTGGCACCGC 1199

916 GTTATTTCAGACTTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG 965
    ||||||||||||||||||||||||||||||||||||||||||||||||
1200 GTTATTTCAGACTTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG 1249

966 TTGCCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC 1015
    ||||||||||||||||||||||||||||||||||||||||||||||||
1250 TTGCCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC 1299

1016 TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCCAACAAGAT 1065
    ||||||||||||||||||||||||||||||||||||||||||||||||
1300 TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCCAACAAGAT 1349

1066 GAGATTCCCTCCAAGTGAAGTTCCAGAGAGACCCGGAAGAGATTATCTGGT 1115
    ||||||||||||||||||||||||||||||||||||||||||||||||
1350 GAGATTCCCTCCAAGTGAAGTTCCAGAGAGACCCGGAAGAGATTATCTGGT 1399

1116 CCATGAGCCCTGTGGTGGATGGTGTGGTGATCCCAGATGACCCTTTGGTG 1165
    ||||||||||||||||||||||||||||||||||||||||||||||||
1400 CCATGAGCCCTGTGGTGGATGGTGTGGTGATCCCAGATGACCCTTTGGTG 1449

1166 CTCCTGACCCAGGGGAAGGTTTCATCTGTGCCCTACCTTCTAGGTGTCAA 1215
    ||||||||||||||||||||||||||||||||||||||||||||||||
1450 CTCCTGACCCAGGGGAAGGTTTCATCTGTGCCCTACCTTCTAGGTGTCAA 1499

1216 CAACCTGGAATTCAATTGGCTCTTGCCTTATATCATGAAGTTCCCGCTAA 1265
    ||||||||||||||||||||||||||||||||||||||||||||||||
1500 CAACCTGGAATTCAATTGGCTCTTGCCTTAT..... 1530

    .
    .
    .

1316 CGCACCCCTGTTGAATATCACCAAGGAGCAGGTACCACTTGTGGTGGAGGA 1365
    ||||||||||||||||||||||||||||||||||||||||||||||||
1531 .....AATATCACCAAGGAGCAGGTACCACTTGTGGTCGAGGA 1568

1366 GTACCTGGACAATGTCAATGAGCATGACTGGAAGATGCTACGAAACCGTA 1415
  
```



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FIG. 3D

1416 TGATGGACATAGTTCAAGATGCCACTTTCGTGTATGCCCACTGCAGACT 1465
|||||
1619 TGATGGACATAGTTCAAGATGCCACTTTCGTGTATGCCCACTGCAGACT 1668

1466 GCTCACTACCACCGAGATGCCGGCCTCCCTGTCTACCTGTATGAATTTGA 1515
|||||
1669 GCTCACTACCACCGA..... 1683

.....

1666 CAACTTTGCCCCGACAGGAAACCCCAATGATGGGAATCTGCCCTGCTGGC 1715
|||||
1684GAAACCCCAATGATGGGAATCTGCCCTGCTGGC 1716

1716 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTTACCACAAGA 1765
|||||
1717 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTTACCACAAGA 1766

1766 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTTTGGATGAGTCTGTA 1815
|||||
1767 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTTTGGATGAGTCTGTA 1816

1816 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1865
|||||
1817 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1866

1866 GGAAGGAGCCAAAGAGGGGTTTGCCCCCACCATCCAGGCCCTGGGGAGAC 1915
|||||
1867 GGAAGGAGCCAAAGAGGGGTTTGCCCCCACCATCCAGGCCCTGGGGAGAC 1916

1916 TAGCCATGGACATACCTGGGGACAAGAGTTCTACCCAAGGGCGAATTCGT 1965
|||||
1917 TAGCCATGGACATACCTGGGGACAAGAGTTCTACCCA...CCCCA...GT 1960

1966 TTAAACCTGCAGGA.CTAG..... 1983
|||
1961 TTAGAACTGCAGGAGCTCCCTGCTGCCTCCAGGCCAAAGCTAGAGCTTTT 2010

.....

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FIG. 4B

160	170	180	190	200	210
COE-2	VWFP	GA	FIV	GA	SSYEGSDLAAREKVVLFQHR
	LGIF	GLST	DDSH	ARGN	WGLLDQMA
	pro873	VWFP	GA	FIV	GA
		SSYEGSDLAAREKVVLFQHR	LGIF	GLST	DDSH
		ARGN	WGLLDQMA		
	250	260	270	280	290
	300				
220	230	240	250	260	270
COE-2	ALRW	VQEN	IAAF	GGDP	GNVTLFG
	QSAG	AMSI	GLMMS	PLAS	GLFHRAISQSGTALFRLFI
	pro873	ALRW	VQEN	IAAF	GGDP
		GNVTLFG	QSAG	AMSI	GLMMS
		PLAS	GLFHRAISQSGTALFRLFI		
	310	320	330	340	350
	360				
280	290	300	310	320	330
COE-2	TSNPL	KVAK	VHLAGCNHNSTQILVNC	RALSGTKVMRVS	NKMRFLQ
	pro873	TSNPL	KVAK	VHLAGCNHNSTQILVNC	RALSGTKVMRVS
	370	380	390	400	410
	420				
340	350	360	370	380	390
COE-2	SMSP	VVDG	VVIP	DDPLVLLTQ	GKVSSVPYLLGVNNLEF
	pro873	SMSP	VVDG	VVIP	DDPLVLLTQ
	430	440	450	460	
400	410	420	430	440	450
COE-2	TKML	WSTR	TLNITKEQ	VLVVEEYLDNVNEHD	WKMLRNRMMDIVQDATFVYATLQTAHY
	pro873				
	470	480	490	500	510



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FIG. 4C

460 470 480 490 500 510
COE-2 HRDAGLPVLYEFEEHHARGIIVKPRTDGADHGDEMYFLFGPPFATGLSMGKEKALSLOMM
::: : : : :
pro873 HRET--PMM-----GIC--P-----AGHA-----
520

520 530 540 550 560 570
COE-2 KYWANFARTGNPNDGNLPCWPRYNKDEKYLQLDFTTRVGMKLKEKKMAFWMSLYQSQRPE
::: : : : :
pro873 -----TTRM-----KSTCSWIL-----P-
530 540

580
COE-2 KQRQF
:
pro873 -QEWA

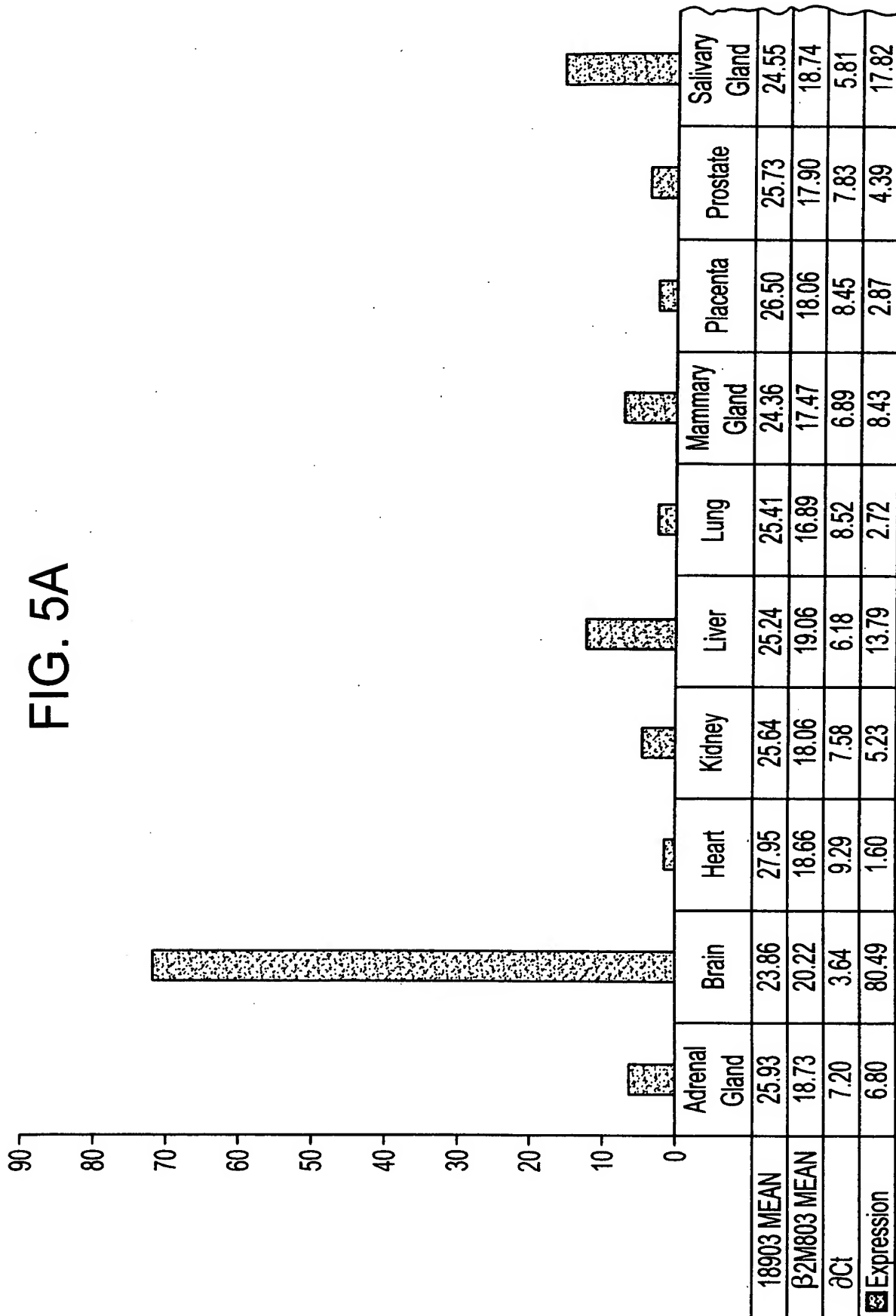


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FIG. 5A





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FIG. 5B

Muscle	Sm. Intestine	Spleen	Stomach	Teste	Thymus	Trachea	Uterus	Spinal Cord	Skin	DRG
29.70	25.43	26.89	26.27	24.29	26.33	25.14	26.18	23.99	23.01	25.06
20.66	17.86	16.37	18.03	19.32	18.19	19.10	18.53	19.20	17.10	19.07
9.04	7.58	10.52	8.25	4.97	8.15	6.04	7.66	4.80	5.91	5.99
1.91	5.24	0.68	3.30	31.91	3.53	15.25	4.96	36.02	16.63	15.73

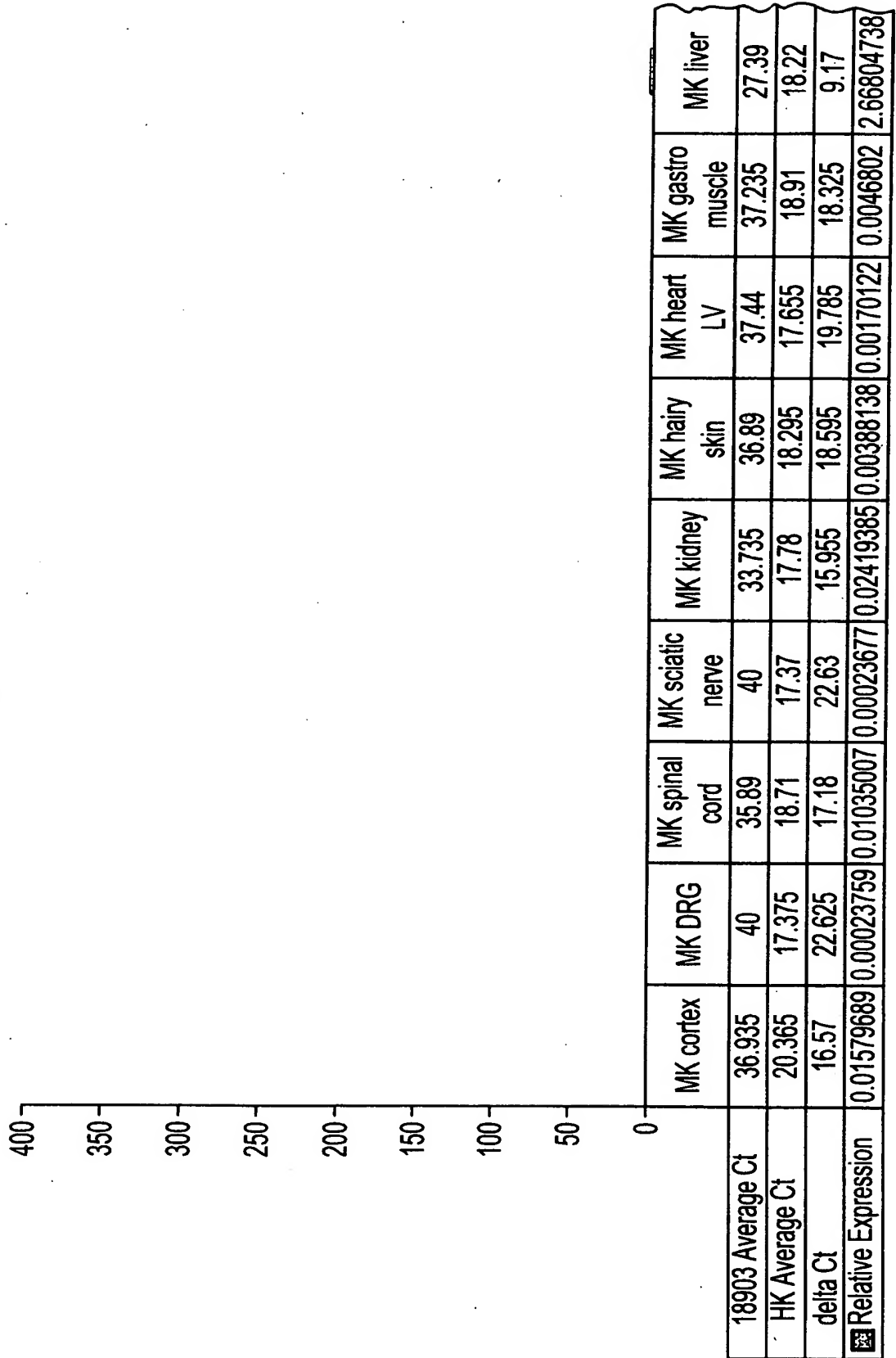


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FIG. 6A





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FIG. 6B

				Hu. Brain	Hu. Spinal cord	Hu. Heart	Hu. Kidney
				Hu. Liver	Hu. Lung		
				21.27	23.78	28.26	26.155
				19.245	18.295	17.855	17.925
				2.025	5.485	10.405	8.23
				377.618146	34.3154004	1.13349992	5.11872423
				10.3803579	1.57002147	9.935	15.87
				25.43	25.805	7.21	25.87

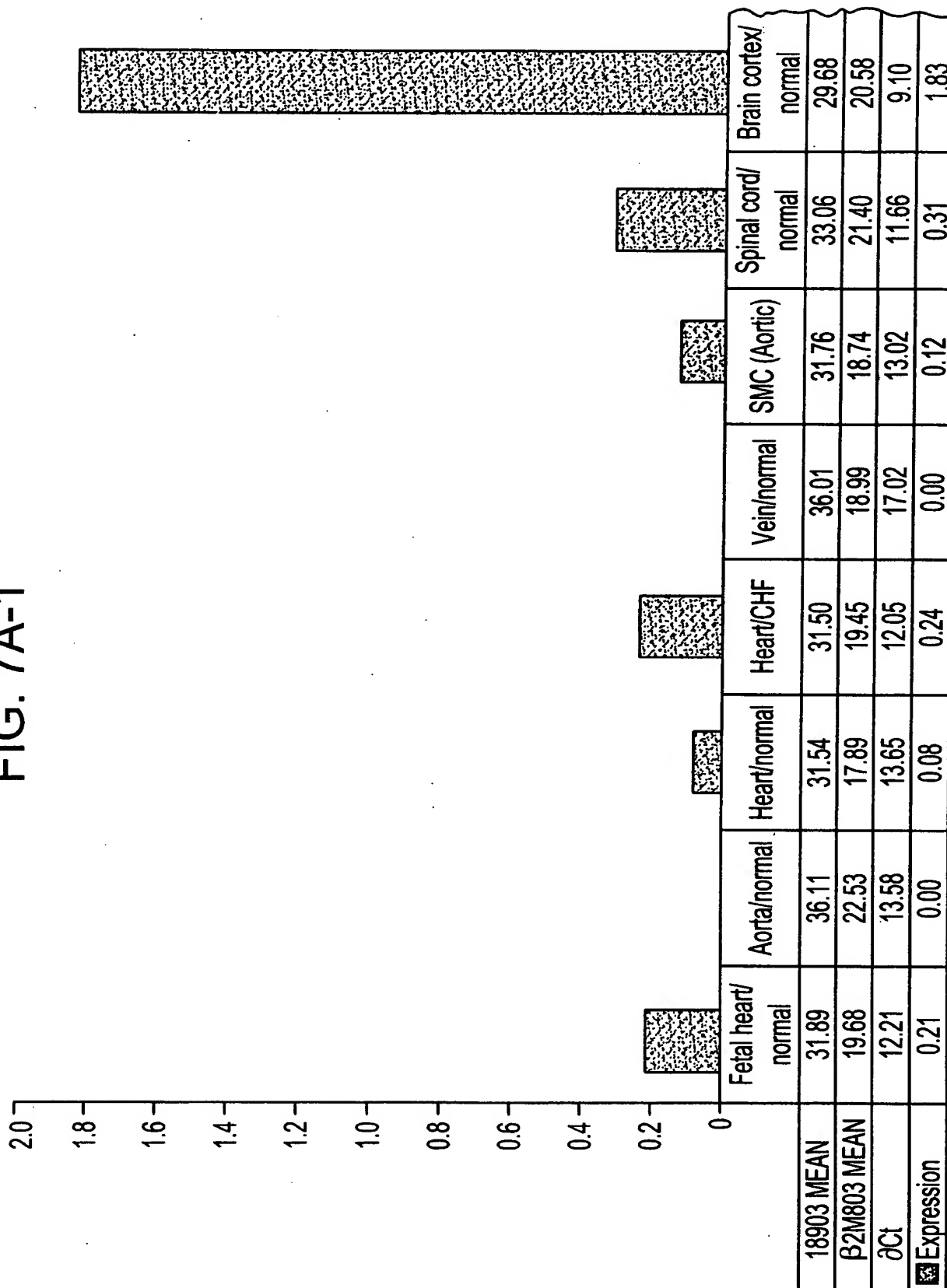


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FIG. 7A-1





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FIG. 7A-2

Brain hypothalamus	Glial cells (Astrocytes)	Brain/ Glioblastoma	Breast/ normal	Breast tumor/ IDC	OVARY/ Normal	OVARY/ Tumor	Pancreas	Prostate/ Normal	Prostate/ Tumor
29.45	33.94	30.39	30.10	30.75	31.73	33.59	30.88	31.16	29.03
19.24	21.09	17.43	18.60	17.66	19.95	18.91	17.33	18.34	17.57
10.21	12.86	12.97	11.50	13.09	11.79	14.68	13.55	12.83	11.46
0.85	0.13	0.13	0.35	0.11	0.28	0.04	0.08	0.14	0.35

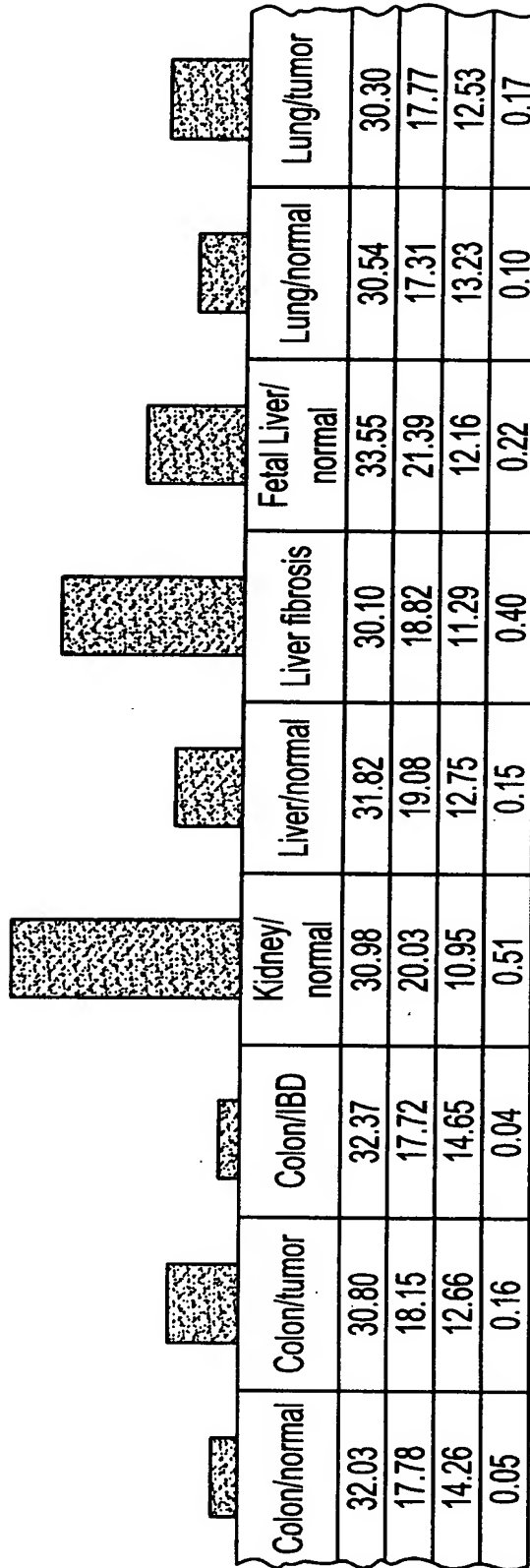


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FIG. 7A-3



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FIG. 7A-4

Lung/COPD	Tonsil/normal	Lymph node/normal	Thymus/normal	Epithelial Cells (Prostate)	Endothelial Cells (Aortic)	Skeletal Muscle	Fibroblasts (Dermal)	Skin/Normal	Adipose/Normal
29.44	31.13	31.40	32.80	30.70	35.27	31.06	33.10	31.16	32.43
17.10	17.19	17.91	20.03	20.13	20.16	18.26	18.18	20.29	17.96
12.34	13.94	13.49	12.78	10.57	15.11	12.81	14.92	10.87	14.47
0.19	0.06	0.09	0.14	0.66	0.03	0.14	0.03	0.54	0.04





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FIG. 7A-5

Osteoblasts (Primary)	Osteoblasts (Undiff)	Osteoblasts (Diff)	Osteoclasts	Aorta SMC (Early)	Aorta SMC (Late)	HUVEC	HMVEC
34.84	33.19	33.23	32.47	32.50	32.72	32.17	32.74
20.44	18.50	17.83	17.25	19.53	18.77	19.27	18.74
14.40	14.69	15.40	15.22	12.97	13.96	12.91	14.00
0.05	0.04	0.02	0.03	0.13	0.06	0.13	0.06



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FIG. 7B

Tissue	18903 MEAN	β 2M803 MEAN	δ Ct	Expression
Fetal heart/normal	31.89	19.68	12.21	0.21
Aorta/normal	36.11	22.53	13.58	0.00
Heart normal	31.54	17.89	13.65	0.08
Heart/CHF	31.50	19.45	12.05	0.24
Vein/normal	36.01	18.99	17.02	0.00
SMC (Aortic)	31.76	18.74	13.02	0.12
Spinal cord/normal	33.06	21.40	11.66	0.31
Brain cortex/normal	29.68	20.58	9.10	1.83
Brain hypothalamus/normal	29.45	19.24	10.21	0.85
Glial cells (Astrocytes)	33.94	21.09	12.86	0.13
Brain/Glioblastoma	30.39	17.43	12.97	0.13
Breast/normal	30.10	18.60	11.50	0.35
Breast tumor/IDC	30.75	17.66	13.09	0.11
Ovary/normal	31.73	19.95	11.79	0.28
Ovary/tumor	33.59	18.91	14.68	0.04
Pancreas	30.88	17.33	13.55	0.08
Prostate/normal	31.16	18.34	12.83	0.14
Prostate/tumor	29.03	17.57	11.46	0.35
Colon/normal	32.03	17.78	14.26	0.05
Colon/tumor	30.80	18.15	12.66	0.16
Colon/IBD	32.37	17.72	14.65	0.04
Kidney/normal	30.98	20.03	10.95	0.51
Liver/normal	31.82	19.08	12.75	0.15
Liver/fibrosis	30.10	18.82	11.29	0.40
Fetal Liver/normal	33.55	21.39	12.16	0.22
Lung/normal	30.54	17.31	13.23	0.10
Lung/tumor	30.30	17.77	12.53	0.17
Lung/COPD	29.44	17.10	12.34	0.19
Tonsil/normal	31.13	17.19	13.94	0.06
Lymph node/normal	31.40	17.91	13.49	0.09
Thymus/normal	32.80	20.03	12.78	0.14
Epithelial Cells(prostate)	30.70	20.13	10.57	0.66
Endothelial Cells(aortic)	35.27	20.16	15.11	0.03
Skeletal Muscle/normal	31.06	18.26	12.81	0.14
Fibroblasts (Dermal)	33.10	18.18	14.92	0.03
Skin/normal	31.16	20.29	10.87	0.54
Adipose/normal	32.43	17.96	14.47	0.04
Osteoblasts (primary)	34.84	20.44	14.40	0.05
Osteoblasts (Undiff)	33.19	18.50	14.69	0.04
Osteoblasts (Diff)	33.23	17.83	15.40	0.02
Osteoblasts	32.47	17.25	15.22	0.03
Aorta SMC (Early)	32.50	19.53	12.97	0.13
Aorta SMC (Late)	32.72	18.77	13.96	0.06
HUVEC	32.17	19.27	12.91	0.13
HMVEC	32.74	18.74	14.00	0.06
	40.00	40.00	0.00	